Antithyroid Drug-induced Agranulocytosis Complicated by Pneumococcal Sepsis and Upper Airway Obstruction

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Abstract

Streptococcus pneumoniae is a rare pathogen of sepsis in patients with antithyroid drug-induced agranulocytosis. We herein describe a case of antithyroid drug-induced agranulocytosis complicated by pneumococcal sepsis and upper airway obstruction. A 27-year-old woman who was previously prescribed methimazole for nine months presented with a four-day history of a sore throat. She nearly choked and was diagnosed with febrile agranulocytosis. She was successfully treated with intubation, intravenous antibiotics and granulocyte colony-stimulating factor. Her blood cultures yielded S. pneumoniae. Emergency airway management, treatment of sepsis and the administration of granulocyte colony-stimulating factor can improve the clinical course of antithyroid drug-induced pneumococcal sepsis in patients with airway obstruction.

Key words: antithyroid agents, agranulocytosis, pneumococcal infection, airway obstruction, granulocyte colony-stimulating factor

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Introduction

Antithyroid drug (ATD)-induced agranulocytosis (an absolute neutrophil count of <500×10^6/L) is rare, developing in only 0.1-1.0% of patients consuming antithyroid drugs (1). However, life-threatening infections reportedly develop in 0.23% of patients with hyperthyroidism treated with antithyroid drugs (2), with a high mortality rate of 5-14% (2, 3). The development of bacteremia is a known predictor of a poor prognosis in patients with drug-induced agranulocytosis (4).

Currently, Gram-negative bacilli, including Pseudomonas aeruginosa and Klebsiella pneumoniae, are the most common pathogens involved in such infections, followed by Escherichia coli and Staphylococcus aureus (2). The occurrence of pneumococcal bacteremia in neutropenic cancer (5) and HIV-infected (6) patients is well known; however, no previous reports have described patients with ATD-induced agranulocytosis complicated by pneumococcal sepsis. We herein report the successful treatment of a patient with ATD-induced agranulocytosis complicated by pneumococcal sepsis and upper airway obstruction.

Case Report

A 27-year-old woman presenting with a four-day history of arthralgia and a sore throat arrived at our hospital by ambulance. She denied having diarrhea or abdominal pain, although she reported dysphagia, dysphonia and salivation. Levofloxacin (LVFX) (500 mg/day) had been prescribed just two days before she visited our hospital. At 20 years of age, she had been diagnosed with schizophrenia and prescribed sodium valproate (400 mg/day), risperidone (2 mg/day), lorazepam (1 mg/day) and estazolam (2 mg/day).

Nine months before admission, she had been diagnosed with Grave’s disease and prescribed methimazole (MMI). She had no history of smoking, alcohol intake or surgery, including splenectomy. She had no sick contact. Seven months earlier, her white blood cell count had been 6,100 cells/mm^3 (normal range: 3,900-9,800 cells/mm^3). However, this parameter decreased to 1,000 cells/mm^3 two days before

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admission. Upon examination, the patient appeared sick and had difficulty breathing with drooling. Her weight was 68.8 kg, her height was 161 cm and her body mass index was 26.5 kg/m\(^2\). Her level of consciousness was E4V2M4 on the Glasgow Coma Scale. Her body temperature was 40.4 \(^\circ\)C, her heart rate was 178 bpm, her blood pressure was 148/84 mmHg, her respiratory rate was 38 breaths/min and her oxygen saturation was 96% while breathing ambient air. In addition, the tonsils were swollen with pus, and the cervical lymph nodes were enlarged bilaterally. Pan-inspiratory stridor was heard in the neck. A cardiac examination revealed normal S1 and S2 sounds. The patient’s abdomen was normal, and there was no peripheral edema. The results of a neurologic examination were unremarkable.

The laboratory findings obtained on admission are shown in Table. The white blood cell count was markedly decreased at 180 cells/mm\(^3\) (normal range: 3,900-9,800 cells/mm\(^3\)) with agranulocytosis. The lactate dehydrogenase level was elevated at 871 IU/L (normal range: 120-240 IU/L). The C-reactive protein level was markedly elevated at 25.6 mg/dL (normal range: <0.30 mg/dL).

Immediately after arrival, we passed a laryngoscope down the patient’s throat into the larynx. A laryngoscopic observation revealed that the upper airway mucosa was markedly swollen with pus from the adenoid to the larynx, with pinhole stenosis in the airway. The epiglottis and larynx were not significantly inflamed. Therefore, the patient was intubated.

Electrocardiography revealed sinus tachycardia with evidence of left-axis deviation. Chest radiography revealed no infiltration. Computed tomography of the neck and chest showed areas of soft tissue density fully wrapping the intra-tracheal tube from the pharynx to the larynx (Fig. 1). A sputum smear with Gram staining revealed Gram-positive diplococci. The results of the Binax Streptococcus Pneumoniae Urinary Antigen Kit (Binax, Portland, ME, USA) were positive. Following admission to the intensive care unit, the patient’s systolic blood pressure decreased to 60 mmHg. Fluid resuscitation with acetated Ringer’s solution was administered. Methimazole was discontinued. Sodium valproate, risperidone, lorazepam and estazolam were continued. In addition to 4 g/day of ceftriaxone (CTRX), 100 μg/day of granulocyte colony-stimulating factor (G-CSF; lenograstim) was administered. Thereafter, the patient’s general condition, blood pressure and laboratory parameters of inflammation gradually improved in parallel with a recovery in the neutrophil count. The administration of G-CSF was continued for six days until the neutrophil count reached 2,000 μ/L on day 7. A blood culture performed on day 8 yielded no microbes. On day 9, the patient was successfully extubated, and the swelling in the upper airway soft tissue improved. On day 15, she developed hyperthyroidism, and we administered 100 mg/day of potassium iodide to control the thyroid function. The patient’s clinical course is summarized in Fig. 2.

### Table. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Complete blood count</th>
<th>Blood Chemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong></td>
<td>180 /μL</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0 %</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>96 %</td>
</tr>
<tr>
<td>Basophils</td>
<td>0 %</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0 %</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3 %</td>
</tr>
<tr>
<td>Hb</td>
<td>11.9 g/dL</td>
</tr>
<tr>
<td>Plt</td>
<td>15.1×10(^4) /μL</td>
</tr>
<tr>
<td><strong>Atrial blood gas</strong></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.427</td>
</tr>
<tr>
<td>PaO(_2)</td>
<td>80.0 torr</td>
</tr>
<tr>
<td>PaCO(_2)</td>
<td>30.4 torr</td>
</tr>
<tr>
<td>HCO(_3)(^-)</td>
<td>19.6 torr</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>+</td>
</tr>
<tr>
<td>Occult blood</td>
<td>-</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>-</td>
</tr>
</tbody>
</table>

| **Sputum smear** | Geckler6 GPDC2+ |
| **Sputum culture** | MSSA |
| **Blood culture** | PSSP |
In this case report, we described the case of a patient with ATD-induced agranulocytosis complicated by pneumococcal sepsis and upper airway obstruction. Antidepressants and antipsychotics were continued during the patient’s clinical course of recovery from agranulocytosis, which argues against a causal relationship between these drugs and agranulocytosis in this case. Neutropenia itself can be caused by serious infections; however, the present patient had none of the following risk factors for sepsis: asplenia, hematologic malignancy, infectious diseases, such as HIV or influenza, or a history of medications, such as high-dose corticosteroids. In cases of neutropenia caused by *Streptococcus pneumoniae* infection, the patient’s condition usually recovers rapidly following the administration of G-CSF (7). However, in this case, it took seven days for the patient to recover from neutropenia, even after receiving G-CSF, another finding that supports our contention that the agranulocytosis preceded the pneumococcal bacteremia. Agranulocytosis usually occurs within two months of the initiation of ATD therapy (8) and is more likely to develop in older patients (>40 years of age) (9) and those receiving higher doses of MMI (30 vs. 15 mg/day) (10). In the present young patient, agranulocytosis developed nine months after the administration of 30 mg/day of MMI; therefore, we believe that the higher dose may have played a role in the pathogenesis of agranulocytosis in this case. Awareness of the possibility for the development of agranulocytosis re-
mains important, even two months after the initiation of ATD-therapy.

Patients with ATD-induced agranulocytosis usually present with fever and a sore throat (11), with the most common clinical diagnoses being acute pharyngitis and tonsillitis (2). Severe pyogenic infections, such as peritonsillar and retropharyngeal abscesses, airway obstruction, pneumonia and acute respiratory distress syndrome may complicate ATD-induced agranulocytosis (2). The possibility for the sudden onset of life-threatening complications warrants the timely diagnosis and appropriate management of these infections. Despite the severe airway obstruction observed in the present case, we successfully treated the patient with emergency airway management and the administration of intravenous antibiotics and G-CSF.

A previous small randomized study suggested that G-CSF does not improve the hematologic recovery from ATD-induced agranulocytosis (12). Meanwhile, G-CSF has been reported to shorten the duration of neutropenia in patients with drug-induced agranulocytosis in other studies (13, 14) and to reduce mortality in a meta-analysis of 118 published reports (15). The present findings also support the effectiveness of G-CSF in treating ATD-induced agranulocytosis.

In the present case, PSSP was identified in blood culture bottles. Although a sputum smear with Gram staining revealed Gram-positive diplococci and the results of the S. pneumoniae Urinary Antigen Kit were positive, the sputum culture yielded no growth of S. pneumoniae. The specificity of sputum smears with Gram staining and the Urinary Antigen Kit is relatively high (16, 17), while the sensitivity of sputum cultures for S. pneumoniae bacteremia is reported to be 79% (18). The rate of culture positivity for S. pneumoniae decreases after antibiotic therapy (19). In the present case, the sputum sample was collected two days after the administration of LVFX. The delay until the assay of the sputum specimen may have resulted in the autolysis of the bacteria, which led to the negative culture result.

In the present case, the patient was initially treated with levofloxacin. The susceptibility of PSSP to levofloxacin was preserved (MIC <1 µg/mL) and found to be similar to that of most current PSSP strains (20). However, the treatment was ineffective under the state of agranulocytosis (5). Although the susceptibility of PSSP to ceftriaxone was preserved (MIC=0.5 µg/mL), the treatment did not demonstrate any clinical effectiveness until the patient recovered from the agranulocytosis. The present case illustrates the significance of a patient’s recovery from agranulocytosis when managing life-threatening infections.

In conclusion, the presence of S. pneumoniae sepsis must be considered in patients with ATD-induced agranulocytosis primarily involving the upper airway. In addition, emergency airway management and the administration of intravenous antibiotics and G-CSF should be provided in patients with ATD-induced agranulocytosis complicated by life-threatening infections.

The authors state that they have no Conflict of Interest (COI).

References

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